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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/931,951	08/20/2001	Nobuhiro Sato	213126US0X	4655

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 09/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/931,951	SATO ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

FINAL ACTION

1. This Office Action is responsive to Applicant's response filed May 26, 2004.

Rejections Maintained

2. The rejection of claims 16-18 under 35 U.S.C. 112, first paragraph is maintained for the reasons set forth on pages 3-8, paragraph 3 of the previous Office Action.

The rejection was on the grounds that claims are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 16-18 are drawn to a method of diagnosis of ulcerative colitis.

The specification is only enabled for a method of detecting *Fusobacterium varium* antibodies and not a method of diagnosis of ulcerative colitis.

There are several factors that contribute to the diagnosis of a disease or disorder that are well known in the art. These factors include: 1) the known etiologic agent that causes the disease, 2) the cross reactivity of multiple microorganisms involved in the disease and 3) the immunopathogenesis associated with the disease. The etiologic agent associated with ulcerative colitis is unknown. This is evidenced by Sartor *(Gasreoenterology Clinic of North America (UNITED STATES), September 1995, 24, p. 475-507).* Sartor teaches that ulcerative colitis and Crohn's disease collectively are referred to as inflammatory bowel disease (IBD), are chronic, spontaneously relapsing disorders of unknown cause (see the Abstract). Braegger *(Acta Paediatr Suppl. 395 : 18021, 1994)* teaches that the etiology and pathogenesis of chronic inflammatory bowel disease are unknown (see the Abstract). Fox et al *(Infection and Immunity, April 1999, p. 1757-1762)* suggest that *Helicobacter* species are associated with colitis (the Abstract). It is unpredictable as to which microorganisms may be involved in ulcerative colitis. This is evidenced by Macpherson et al *(Gut, 1996,38:365-375).* Macpherson et al suggest that there may be multiple organisms involved in inflammatory bowel disease. Macpherson et al disclose experiments that show that in relapse of inflammatory bowel disease there is a breakdown of tolerance to the normal commensal flora of the gut (which includes multiple organisms). Multiple microorganisms that reside in

the gastrointestinal tract are evidenced by Coleman et al, *(Applied and Environmental Microbiology, October 1996, p. 3632-3639).* Coleman et al teach that there are six microbial competitors in the human gastrointestinal tract and they are *Escherichia coli, Enterobacter aergenes*, *Bacteroides ovatus, Fusobacterium varium* and *Enterococcus faecalis*. Cross-reactivity is a factor to be considered since there are multiple microorganisms that reside in the gastrointestinal tract. Marx et al *(Infection and Immunity, June 1982, 36 (3) p. 943-948)* teach that cross-reactivity exist between species of the genera *Bacteroides* and species of the genera *Fusobacterium* (see the Abstract). Ushijima et al *(Journal of Medical Microbiology, September 1990, 33 (10:17-22)* further teach that cross-reactivity exists between species of colonic bacteria (see the Abstract). Immunopathogenesis is also associated with ulcerative colitis. Braegger *(Acta Paediatr Suppl. 395 : 18021, 1994)* teaches that immunological mechanisms may play a significant role in mediating the intestinal lesion and some of the systemic manifestations of Crohn's disease and ulcerative colitis. Braegger teaches that Crohn's disease and ulcerative colitis present dense infiltration of inflammatory cells, increased plasma cells, T lymphocytes, macrophages and neutrophils (page 18, 1st column). Braegger further teaches that ulcerative colitis may be caused by an IgG-mediated autoimmune process to the colon mucosa (pages 20-21).

Since the detection of antibodies is used in the claimed invention to diagnose ulcerative colitis, one skilled in the art would have to possess the knowledge or be provided with sufficient guidance with regard as to how to detect only the target microorganism (i.e. *Fusobacterium varium*) and not a mixture of colonic bacteria antibodies in order to make a diagnosis of ulcerative colitis. The cited references have shown that unpredictability and uncertainty exists regarding which microorganism or microorganisms are the causative agents of ulcerative colitis. Other references have been cited that show that there are multiple microorganisms that reside in the gastrointestinal tract and references have also been cited to show the immunopathogenesis associated with the disease. Therefore, it can be concluded that undue experimentation would be required to use the claimed method of diagnosing ulcerative colitis without proper guidance.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention.

The specification fails to teach how a sample is obtained? How to determine the amount of antibody significant to make a diagnosis of ulcerative colitis? How to assure that the target antibody (i.e. *Fusobacterium varium*) is obtained and not a mixture of antibodies from other colonic bacteria? Nor does the specification provide a correlation between how to diagnosis of ulcerative colitis and the detection of *Fusobacterium varium* antibodies. Therefore, it is unclear as to how to make a diagnosis of ulcerative colitis using the claimed method.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the

quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification as to the etiologic agent that causes ulcerative colitis 3) there are limited working examples which suggest the detection of *Fusobacterium varium* antibodies 4) the relative skill of those in the art is commonly recognized as quite high (post - doctoral level), and the lack of predictability in the field to which the invention pertains is recognized in the art as evidenced by the cited prior art.

In view of all of the above, in view of the lack of predictability regarding the cross reactivity of microorganisms that inhabit the gastrointestinal tract and uncertainty of the etiologic agent of ulcerative colitis in the art, it is determined that it would require undue experimentation to use the claimed invention.

Applicant urges that claim 16 has been amended to specifically indicate that the classification of ulcerative colitis sought to be diagnosed is "ulcerative colitis caused by *Fusobacterium varium*". Applicant urges that the skilled artisan could easily carry out the claimed method by using either a western blotting method or an enzyme-linked immunosobent assay (ELISA) with the present specification in hand. Applicant urges that Example 1 of the specification clearly shows that Fusobacterium varium can be readily isolated and an antibody specific thereto can be obtained. Applicant urges that the alleged deficiencies in the specification would be well within the purview of routine experimentation by the skilled artisan. Applicant urges that the Ohkusa et al reference has established a clear indication of a causal relationship between *Fusobacterium varium* and ulcerative colitis. Applicant urges that Ohkusa et al demonstrate a proof of principal and doing so support the inventive method for making a

diagnosis of ulcerative colitis caused by *Fusobacterium varium* in a patient which comprises obtaining sera from a patient; detecting an antibody specific for *Fusobacterium varium* in said serum and correlating the presence of an antibody specific for *Fusobacterium varium* in said sera with ulcerative colitis. Applicant urges that specifically, Ohkusa et al demonstrate that only sera from patients with ulcerative colitis gave specific reactions with *Fusobacterium varium* in Western blot assays from a collection of patients suffering from active ulcerative colitis, Crohn's disease, ischemic colitis and colon adenomas. Applicant urges that Ohkusa et al demonstrate the combination of IgG, IgA, and IgM as well as either IgG or IgA alone gave higher mean OD for patients with active ulcerative colitis than for Crohn's disease or healthy controls. Applicant urges that Ohkusa et al demonstrate that *Fusobacterium varium* was detected immunohistochemically in the exudates, surface mucus and crypts of the colonic mucosa in 84% of patients with active UC and in contrast only 13% of the patients in remission from UC, 16% of patients with Crohn's disease, 13% of patients with ischemic colitis and 3% of patients with colon adenoma gave positive immunostaining reactions and the antibody was determined to be specific for *Fusobacterium varium*. Applicant urges that Colman et al does not relate to an antibody response to *F. varium* and therefore it is unclear how this reference directly related to the present invention. Applicant urges that Ohkusa et al (Gut 2003, 52:79-83) teach fecal bacteria from ulcerative colitis patients and tested the same for cytotoxicity to Vero cells and determine whether the toxin induces ulcerative colitis –like lesion in animals. Applicant urges that Table 1, page 80, (Ohkusa, 2003) shows that 20 species

obtained from 42 isolates only *Fusobacterium varium* proved to be cytotoxic to Vero cells. Applicant urges that 24 hours after mice were given enemas containing butyric acid or *Fusobacterium varium* culture supernatants colonic ulcers with crypt abscesses, inflammatory cell infiltration and apoptotic changes were observed. Applicant urges that the presence of *Fusobacterium varium* in sera may be used as a diagnostic marker of ulcerative colitis. Applicant urges that the present invention is enabled as defined by 35 U.S.C. 112, first paragraph.

Applicant's arguments filed May 26, 2004 have been fully considered but they are not persuasive. It is the Examiner's position that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention. The prior art cited above and Ohkusa et al agree that the etiology of ulcerative colitis is unknown but the disease shares histological features with colitis caused by infectious agents (page 849). Ohkusa et al teach that *Fusobacterium varium* antibodies where detected in 61% of patients with active UC opposed to 13% of patients with Crohn's disease and 29% of the healthy control patients (page 850). Ohkusa et al teach that the detection of serum antibodies to *F. varium* has the potential to become a differential diagnosis marker in inflammatory bowel disease (page 852). The specification teaches that "in an ELISA and immunohistochemistry with *F. varium* proteins an (as) antigen, mean optical density and the detection rate were higher for our patients than for subjects with Crohn's disease or other controls" (page 8, Example 1). Although, Coleman et al, *(Applied and*

Environmental Microbiology, October 1996, p. 3632-3639) do not teach detection of *F. varium* antibodies, the Coleman et al reference is used to teach that *F. varium* are among six microbial competitors that reside in the human gastrointestinal tract. One of skill in the art would expect that *Fusobacterium varium* would be detected in healthy individuals as well as individuals suffering from an inflammatory bowel diseases. Therefore, if *F. varium* resides in the human gastrointestinal tract of healthy individuals and *F. varium* resides in the human gastrointestinal tract of individuals with UC as well as other inflammatory bowel diseases, how could the detection of *F. varium* be used as a diagnostic marker for UC? One of skill in the art cannot conclude that the detection of *Fusobacterium varium* is a diagnostic maker for ulcerative colitis since antibodies of *Fusobacterium varium* were detected in other inflammatory bowel diseases and as well as in healthy individuals (controls). Ohkusa et al may have established that there appears to be a relationship between *F. varium* and ulcerative colitis since a high number of *F. varium* antibodies were detected in UC patients. However, Ohkusa et al have not established that *Fusobacterium varium* is the causative agent of ulcerative colitis nor has the instant specification established that *Fusobacterium varium* is the causative agent of ulcerative colitis. To address Applicant's comments regarding Ohkusa et al (Gut, 2003), it should be noted that Ohkusa et al, 2003 states that "the aetiology of ulcerative colitis (UC) is unknown (page 79). Ohkusa et al, 2003 teach that patients with UC have abnormally large numbers of facultative anaerobic bacteria (page 79). Ohkusa et al, 2003 suggests that *F. varium* invades the mucus and mucosa and live in

crypts of patients with UC and Ohkusa et al, 2003 also states that *H. pylori* can be found in the gastric mucosa. Ohkusa et al, 2003 teach that *F. varium* is toxic to Vero cells and may be one of the pathogenic in UC not the *F. varium* can be used to diagnose UC. One of skill in the art could not conclude that *F. varium* is a diagnostic marker for UC based on the teachings of Ohkusa et al, 2002 or Ohkusa et al, 2003. The instant specification is not enabled for a method for making a diagnosis of ulcerative colitis caused by *Fusobacterium varium* in a patient since the causative agent of UC remains unknown as disclosed by Ohkusa et al, 2002 and Ohkusa et al, 2003 as well as the above cited art. The specification has failed to provide the guidance needed for the skilled artisan to use the claimed method in a manner that is commensurate with the claims. Therefore, it can be concluded that undue experimentation would be required to use the claimed method of diagnosing ulcerative colitis caused by *Fusobacterium varium* without proper guidance.

3. The rejection of claims 16-18 under 35 U.S.C. 112, second paragraph is maintained for the reasons set forth on pages 2-3, paragraph 2 of the previous Office Action.

The rejection was on the grounds that the claims rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: 1) providing a sample (i.e. sample source, 2) determining that the target antibody (i.e. *Fusobacterium varium*) is obtained and not antibodies to a mixture of colonic bacteria, 3) determining the amount of antibody significant to make a diagnosis and 4) the correlation as to how to a diagnose of ulcerative colitis is made using the antibody.

Applicant disagrees with the Examiner with respect to omission of essential method steps. Applicant urges that the ability of the skilled artisan to practice the claimed invention is directly related to the fact that the alleged omitted steps are embraced by the claims as presented. Applicant urges that the omitted steps are inherently embraced by the step for detecting an antibody specific for *Fusobacterium varium* in said sera. Applicant refers to page 9 of the instant specification to show that the essential method steps are embraced by the claimed method.

Applicant's arguments filed May 26, 2004 have been fully considered but they are not persuasive. The claims are incomplete for omitting essential steps. Example 1, page 9 of the instant specification merely shows that a western blot and an ELISA were preformed. There is no disclosed of for example, how were the ELISA and Western blotting methods used, were whole *Fusobacterium varium* organisms used to detect antibodies or were proteins of *F. varium* (antigens) used in the assays? Were serum antibodies detected only in patients with UC? Were there antibodies detected in serum from patients with other diseases such as Crohns disease? If so, were the amounts of antibodies detected in UC patients significantly different from patients with other diseases? How does the detection of antibodies to *Fusobacterium varium* correlate to the diagnosis of UC and not other diseases, if antibodies to *F. varium* were found in patients with other diseases? What is the distinction? Essential steps are absent for the claimed method of diagnosing ulcerative colitis caused by *F. varium*. It is

the Examiner's position that claims 16-18 are indefinite and do not meet the requirement of 35 U.S.C. 112, second paragraph.

Status of Claims

4. No claims allowed.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

6. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
August 24, 2004

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